Recommended Principles of Antiretroviral Therapy in HIV Disease

Scientific Committee on AIDS and STI (SCAS),
Centre for Health Protection,
Department of Health

February 2011

Scientific Committee on AIDS and STI (SCAS)
has the following terms of reference :

(a) to advise the Controller of the Centre for Health Protection (CHP) on the scientific basis for the prevention, care and control of HIV/AIDS and STI in Hong Kong;
(b) to develop recommendations and guidance regarding HIV/AIDS and STI in Hong Kong; and
(c) to keep under review local and international development of HIV/AIDS and STI.

Membership 2010-2013

Chairman :	Prof	LAM Tai-hing, JP
Members :	Dr	FAN Yun-sun, Susan
	Dr	HO King-man
	Dr	KAM Kai-man
	Dr	LAI Sik-to, Thomas
	Dr	LEE Chin-peng
	Prof	LEE Shui-shan
	Dr	LI Chung-ki, Patrick, BBS
	Dr	LIM Wei-ling, Wilina, SBS, JP
	Dr	TAM Cheuk-ming
	Dr	TSANG Tak-yin, Owen
	Dr	WONG Ka-hing
	Dr	YAM Wing-cheong
Secretary :	Dr	CHAN Chi-wai, Kenny
Co-Secretary :	Dr	SU Chee-wei, Robin
Secretariat :	Mr	NG Chun-kit, Kenneth

Correspondence
Address : 3/F, Wang Tau Hom Jockey Club Clinic
200 Junction Road East, Kowloon, Hong Kong
Tel : (852) 3143 7281
Fax : (852) 2337 0897
E-mail : aca@dh.gov.hk

Introduction

In 2005, the predecessor of this Committee, Scientific Committee on AIDS, published its set of recommended principles of antiretroviral therapy to provide general guidance for the use of antiretrovirals in Hong Kong. The document stated nine major principles of antiretroviral use.[1]

2. Since then, progress has been made in the realm of HIV management. There have also been corresponding changes in local practice. This Committee therefore undertook to re-examine the document with a view to updates where appropriate. As before, the effort focussed on major principles rather than details of antiretroviral use.

3. The Committee finds that the major principles continue to hold. Nevertheless, it sees the need of updates in the following:

- a new goal of viral suppression even in those with multi-class resistance
- use of HAART in post-exposure prophylaxis and prevention of mother-to-child transmission
- the use of CD4 count as an indication of treatment
- vigilance with adverse effects of HAART

Recommended Principles

I. Highly active antiretroviral therapy (HAART) with potent and durable viral suppression to undetectable levels is the preferred therapy under most clinical circumstances.

4. For practical purposes, HAART may be defined as therapy which is potent enough to suppress HIV viraemia to undetectable levels, as measured by the most sensitive assay available, and which is durable in its virologic effect. Operationally defined as such, HAART implies the need of viral load for monitoring of efficacy.[2] Failure of full virologic suppression or rebound from undetectability calls for immediate review of the regimen.

5. Conventionally HAART includes three or more drugs from at least two classes. However, as long as a regimen can achieve full and durable suppression of viral load, it should be regarded as HAART, regardless of its

composition. On the other hand, known suboptimal regimens, e.g. monotherapy, double nucleoside, or certain triple nucleoside combinations are not HAART and are generally inappropriate in HIV disease.

6. The goal of potent and durable viral suppression is paramount whether the treatment is the initial or subsequent regimen. A failing regimen requires replacement with at least two, or preferably three new drugs without cross resistance to achieve viral suppression. To this end, testing for resistance is useful.[3]

7. In recent years, the number of drug classes and individual drugs has expanded, most of which are available in Hong Kong. The new antiretrovirals, by virtue of their novel mechanisms of action or unique resistance profiles, confer activity against previously resistant viruses. Some of these drugs are also endowed with good tolerability profile. All in all, treatment against multi-class resistant viruses is now more effective and complete viral suppression in what used to be salvage therapy is now possible and should be the new treatment goal. This optimism, however, should be guarded as resistance can evolve if antiretrovirals are not carefully used or if the current emphasis on adherence is not maintained.

8. In Hong Kong, HAART is recommended for postexposure prophylaxis for maximal benefit.[4, 5] In prevention of mother-to-child transmission, HAART incorporating zidovudine is also preferred when the diagnosis is made antenatally, regardless of the state of maternal disease. Lesser therapy however is justifiable when given to the newborn as prophylactic regimen.[6]

II. The initiation of antiretroviral therapy is a decision based on a thorough medical evaluation and informed discussion with the patient.

9. Symptomatic HIV infection, including AIDS-defining conditions and category 'B' symptoms[7] warrants expeditious initiation of HAART. In primary HIV infection, there are also theoretical advantages of immediate treatment which are being evaluated in clinical trials.

10. In chronic, asymptomatic HIV infection, the CD4 'threshold' of treatment initiation has been a moving target. It has ranged from the early

concept of hitting hard and early[8] without regard to the CD4 count, to the current consensus of 350/ul.[9,10,11] As new data from clinical studies continue to emerge, this may be subject to further change. In addition, certain conditions such as pregnancy, hepatitis B co-infection requiring treatment, and HIV-associated nephropathy are now considered to indicate HAART even in the presence of a high CD4. With some patients, the added advantage of reducing onward sexual transmission may also be an important factor of treatment consideration.[12] All in all, it cannot be overemphasised that at any time reference should be made to the best available evidence before initiating treatment.

11. It is not uncommon that a patient is opposed to treatment even when clinically indicated, especially when he is asymptomatic or in the immediate period after diagnosis. While a patient's wishes should be respected at all times, the physician should strive to ensure that he has been apprised of all relevant clinical evidence and the long term advantages of treatment, and that his concerns of therapy are fully addressed. In other words, the decision to delay as well as initiate treatment should be informed.

III. The design of a regimen should take into consideration factors related to the patient as well as the virus, with long term disease control as a major goal.

12. As the availability of antiretrovirals expands, the number of possible combinations multiplies, many of which qualify as HAART because of its virologic potency and durability as shown in clinical trials. However, all regimens do not perform equally for a patient. Furthermore, antiretroviral therapy is long term and potentially carries serious adverse effects. It is therefore imperative that a regimen be individualised, after assessment of the following:

- possibility of unfavourable drug interactions,
- host factors that may hinder adherence, e.g. irregular working hours, depression, gastrointestinal disturbance, etc,
- viral factors that will suggest resistance, e.g. acquisition of HIV from a partner on treatment, and
- underlying risk factors or disease that will predispose to adverse effects of treatment, e.g. cardiovascular risk factors, metabolic syndrome, diarrhoea,

etc.

13. The regimen itself is then optimised in frequency of administration, convenience and pill burden, before it is recommended to the patient. This process is done to facilitate the design of a regimen and not to exclude certain patients from treatment. Assessment should be repeated during subsequent followup, with a view to timely adjustment to achieve long term control of disease.

IV. The offer of antiretroviral therapy is not dependent on predicted adherence. Anticipated difficulties in adhering to a regimen are proactively and empathically managed by appropriate selection of antiretrovirals, intensive counselling and disease monitoring, and correction of factors contributing to non-adherence.

14. There is no overstating the importance of adherence in the successful use of HAART.[13] Certain lifestyle factors are conventionally believed to be associated with non-adherence, most notable of which are substance dependence and commercial sex work. However, data supporting such associations are conflicting and their predictability of nonadherence is crude.[14] Of note, it has been shown that doctors' own prediction of adherence could be poor.[15]

15. Recommendation for antiretroviral therapy should therefore be based solely on medical considerations. Although patient assessment includes that of factors contributing to nonadherence, the objective is to proactively correct these factors before and during antiretroviral use.[16] Depending on circumstances, it may be appropriate to intensify monitoring of adherence[17] and disease, and institute preventive measures against adverse effects. Antretrovirals should be selected in ways conducive to long term adherence which is to be actively monitored in all subsequent clinical encounters. Regardless, it is unacceptable to withhold treatment or prescribe suboptimal therapy because of expected noncompliance.[18]

V. Highly active antiretroviral treatment is but one of a whole array of medical therapies of HIV disease, the other components being effective infection prophylaxis, nutritional therapy, and immunisation.

16. The success of HAART may have overshadowed other interventions that have shown proven clinical benefit. These include but are not limited to correction of anaemia, appropriate prophylaxis against opportunistic infections, nutritional therapy, and certain behavioural modifications that avoid contact with pathogens.[19] Although treatment of latent tuberculosis probably does not prolong survival, the reduction in morbidity also justifies its use in HIV infected patients.[20] Where appropriate, these measures should be combined with HAART.

17. On the other hand, immune recovery by HAART may lead to paradoxical exacerbation and unique presentations of disease.[21,22] In addition, adverse effects associated with long term use of antiretrovirals including fat redistribution and metabolic complications are now recognised. A heightened risk of cardiovascular disease also exists, especially with certain antiretrovirals. It is therefore important that the HIV physician be vigilant to these changes and adopts a comprehensive approach toward disease management if the full potential of HAART were to be realised.

18. Immunisation is available against infections that share similar routes of infection, e.g. hepatitis B, and against infections that may opportunistically infect HIV-positive patients, e.g. influenza and pneumococcus. They should be considered in HIV infected patients.

VI. Novel antiretroviral therapy should be used only in a clinical trial setting where the patient understands the rationale and design of the trial, his potential gains from enrolment, possible adverse effects, and his right to withdraw at any point of time.

19. The rapid advancement of HIV medicine has witnessed unexpected drug interactions and reversal of recommendations. The lesson of caution is thus obvious in the use of novel combinations and novel drugs. A properly conducted clinical trial setting is most appropriate should such therapy be contemplated.

20. Use of novel agents or novel use of available agents is based on potential gains over established therapy. This situation is exemplified by the occurrence in some patients of multiple drug resistance where there is no standard salvage therapy. In a clinical trial setting, the overriding principle is

that a patient should only enrol after fully understanding its implications – especially the potential benefits to the patient and potential adverse effects with new treatment. Such studies should be administered according to the Declaration of Helsinki [23] and after proper evaluation of their ethical implications. Mechanisms of data monitoring and its regular review should be in place, detailed records should be kept, and informed consent be properly obtained. Should new relevant data or opinions emerge in the course of a study, they should be made known to the patients as soon as possible, even if this encourages them to withdraw from the study.

VII. HIV infection is not only a multi-organ disease but beset with enormous social implications. It can be successfully managed only by a multispecialty and multidisciplinary approach, with sensitivity and empathy.

21. HIV infection transcends organ systems and requires management by a multispecialty effort. Experts in antiretroviral therapy should collaborate with specialists of other disciplines, including ophthalmologists, surgeons, neurologists, psychiatrists, gynaecologists, dermatologists, paediatricians and primary care internists. Assistance of other professionals like medical social workers, counsellors, nutritionists and occupational therapists is also essential to a holistic, client-centred approach.

22. Intangible barriers to effective treatment exist in our society in the form of social marginalisation, although attempts are ongoing to eradicate all forms of discrimination against HIV-infected patients. [24] Until then, the physician should be sensitive to such dynamics and be empathic in rendering care. Issues such as confidentiality, unprejudiced medical management, equitable access to care, and partner notification are particularly relevant.

VIII. Long term antiretroviral therapy should be prescribed only by physicians competent in the management of HIV disease, and in settings organised for optimal care.

23. The complexity of antiretroviral treatment, the lifelong commitment of patients to such therapy, and the unforgiving nature of drug resistance mandate prescription only by competent physicians. Currently, the high cost of medications practically limits prescription privileges to physicians of

designated HIV clinics in Hong Kong. However, as availability improves and cost decreases, there is a risk of inappropriate use and emergence of resistance, in a scenario reminiscent of antibiotics.

24. This Committee supports attempts to define qualities of practitioners required for appropriate prescription of antiretrovirals for the long term management of HIV disease. Such attempts should take into account the knowledge base of the physician, his experience and record of care of HIV patients, and evidence of continuing medical education.

25. It is also important that antiretrovirals be used in a setting where there is adequate laboratory support, especially in regard to the measurements of viral load and CD4 count, and testing of drug resistance. There should also be access to consultations with other medical specialties and assistance by other professionals required for optimal care.

26. Short-term antiretroviral use is indicated in post-exposure prophylaxis and occasionally in prevention against mother-to-child transmission, sometimes on an urgent basis. Nevertheless, appropriate prescribing is still important in these circumstances. Therefore, the prescribing physician should either be qualified in antiretroviral use, or have access to expert advice. A peer-reviewed protocol should be available in settings where such use of antiretrovirals is conceivable, e.g. the Accident and Emergency Dept.

IX. While experience of antiretroviral use in overseas countries provides useful guidance, it is desirable that a local, systematized surveillance system is in place for monitoring of efficacy and unexpected adverse effects.

27. Most pre-licensure data on antiretrovirals were obtained in developed countries from studies on ethnic groups other than Chinese. Experience has shown that ethnicity may play a role in the incidence and pattern of adverse effects,[25,26] as well as the very immunologic profile.[27] Local viral factors such as primary resistance may also be relevant. In addition, postmarketing surveillance has uncovered adverse effects never encountered before licensure.[28]

28. It is thus a matter of principle that surveillance for adverse effects and

antiviral efficacy be carried out despite drug licensure locally or abroad. It is also desirable that such collection of data be done in a systematic manner.

References

[1] Scientific Committee on AIDS. Recommended principles of antiretroviral therapy in HIV disease Jan 2005 (Available at http://www.info.gov.hk/aids/pdf/g138.pdf. Accessed 25 Oct 2010)

[2] Tarwater PM, Gallant JE, Mellors JW, et al. Prognostic value of plasma HIV RNA among highly active antiretroviral therapy users. AIDS 2004;18:2419-23

[3] Tural C, Ruiz L, Holtzer, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. AIDS 2002;16:209-18

[4] Scientific Committee on AIDS and STI and Infection Control Branch, CHP, DH (2007). Recommendations on the postexposure management and prophylaxis of needlestick injury or mucosal contact to HBV, HCV and HIV. (Available at http://www.info.gov.hk/aids/pdf/g198.pdf. Accessed 25 Oct 2010)

[5] Scientific Committee on AIDS and STI (2006). Using antiretrovirals for post exposure prophylaxis against HIV in the non-occupational setting – position statement of the SCAS (Available at http://www.info.gov.hk/aids/pdf/g160.pdf. Accessed 25 Oct 2010)

[6] Scientific Committee on AIDS and STI. Recommended clinical guidelines on the prevention of perinatal HIV transmission Jan 2007 (Available at http://www.info.gov.hk/aids/pdf/g176.pdf. Accessed 25 Oct 2010)

[7] Scientific Committee of the Advisory Council on AIDS. Classification system for HIV Infection and surveillance case definition for AIDS in adolescents and adults in Hong Kong (Available at http://www.aids.gov.hk. Accessed 18 Oct 2010)

[8] Ho DD. Time to hit HIV, early and hard. N Engl J Med. 1995; 333:450-1

[9] Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. 10 Jan, 2011; 1–166. (Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 11 Jan 2011)

[10] European AIDS Clinical Society. Guidelines, clinical management and treatment of HIV-infected adults in Europe (Available at http://www.europeanaidsclinicalsociety.org/guidelinespdf/1_Treatment_of_HIV_Infected_Adults.pdf. Accessed 25 Oct, 2010)

[11] British HIV Association Guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008. HIV Med 2008;9:563-608

[12] Wilson DP, Law MG, Grulich AE, et al. Relation between HIV viral load and infectiousness: a model-based analysis. Lancet. 2008;372:314-320

[13] Press N, Tyndall MW, Wood E, Hogg RS, Montaner JS. Virologic and immunologic response, clinical progression, and highly active antiretroviral therapy adherence. J Acquir Immune Defic Syndr 2002;31 Suppl 3:S112-7

[14] Palepu A, Tyndall M, Yip B, O'Shaughnessy MV, Hogg RS, Montaner JS. Impaired virologic response to highly active antiretroviral therapy associated with ongoing injection drug use. J Acquir Immune Defic Syndr 2003;32:522-6

[15] Gross R, Bilker WB, Friedman HM, Coyne JC, Strom BL. Provider inaccuracy in assessing adherence and outcomes with newly initiated antiretroviral therapy. AIDS 2002;16:1835-7

[16] Fong OW, Ho CF, Fung LY, et al. Determinants of adherence to highly active antiretroviral therapy (HAART) in Chinese HIV/AIDS patients. HIV Med 2003;4:133-8.

[17] Ho CF, Fong OW, Wong KH. Patient self-report as a marker of adherence to

antiretroviral therapy. Clin Infect Dis 2002;34:1534-5
[18] Tchetgen E, Kaplan EH, Friedland GH. Public health consequences of screening patients for adherence to highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001;26:118-29
[19] US CDC, NIH, IDSA. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Aldolescents. MMWR 2009;58(RR4)
[20] Akolo C, Adetifa I, Shepperd S, et al. Treatment of latent tuberculosis infection in HIV infected persons. Cochrane Database Syst Rev 2010;1:CD000171
[21] French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. AIDS 2004;18:1615-27
[22] Wong KH, Chow WS, Lee SS. Clinical hyperthyroidism in Chinese patients with stable HIV disease. Clin Infect Dis 2004; 39:1257-59
[23] World Medical Association. Declaration of Helsinki. (Available at http://www.wma.net/en/30publications/10policies/b3/17c.pdf. Accessed 25 Oct 2010)
[24] Committee on Promoting Acceptance of People Living with HIV/AIDS, Hong Kong Advisory Council on AIDS. Setting the agenda of promoting acceptance of people living with HIV/AIDS in Hong Kong - a strategy paper, 2001. (Available at http://www.info.gov.hk/aids/pdf/g85.pdf. Accessed 25 Oct 2010)
[25] King J, Aberg JA. Clinical impact of patient population differences and genomic variation in efavirenz therapy. AIDS 2008;22:1709-17
[26] Orkin C, Sadiq ST, Rice L, et al. Prospective epidemiological study of the prevalence of human leukocyte antigen (HLA)-B*5701 in HIV-1-infected UK subjects. HIV Med 2010;11:187-92
[27] Kam KM, Wong KH, Lee SS. Interpretation of CD4+ T-lymphocyte values in different HIV-infected populations [letter]. J Acquir Immune Defic Syndr 1998;17:185-6
[28] Ly T, Ruiz ME. Prolonged QT interval and torsades de pointes associated with atazanavir therapy. Clin Infect Dis 2007;44:e67-8